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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/538,248	03/29/2000	David A. Cheresh	TSRI-651.3	6166

2387 7590 08/13/2004

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/538,248	CHERESH ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,17-20,32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,17-20,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 5-16 and 21-31 have been canceled. Claims 1-4, 17-20 and newly presented claims 32 and 33 are still at issue and are present for examination.

Applicants' arguments filed on 5/17/04, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 17, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Calderwood et al. (US Patent 6,001,839). The rejection is explained in the previous Office Action.

Applicants argue that the Calderwood et al. patent teaches that certain pyrrolopyrimidine compounds are useful for treating VEGF mediated edema but does not teach or suggest that the

pyrrolopyrimidine compounds are inhibitors of human c-src. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivity and activity depending on the spatial arrangement of substituents. This is not persuasive because Calderwood et al. clearly teach the use of each of the specific compounds listed in columns 7-10 for the treatment of VEGF-mediated edema. This list includes the specific compounds 7-isopropyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, (column 9, lines 7-8), 5-[4-(4-aminophenoxy)phenyl]-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (column 9, lines 32-33), and 5-[4-(3-aminophenoxy)phenyl]-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (column 9, lines 34-35), which Burchat et al. (2000) evidence are src kinase inhibitors (see Table 2). As such the pharmaceutical compositions of these specific compounds taught by Calderwood et al. and methods of treating edema using these specific compounds taught by Calderwood et al. anticipate the instant claims.

Claims 1, 2, 17, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Calderwood et al. (US Patent Application 2003/0187001). The rejection is explained in the previous Office Action.

Applicants argue that the Calderwood et al. patent teaches that certain pyrrolopyrimidine compounds are useful for treating VEGF mediated edema but does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-src. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivity and activity depending on the spatial arrangement of substituents. This is not persuasive because Calderwood et al. clearly teach the use of each of the specific compounds of examples for the treatment of VEGF-mediated edema. These examples include the specific compounds 4-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzyl Alcohol, (paragraph 0482), 2-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzyl Alcohol (paragraph 0495), 4-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile (paragraph 0439) and 2-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile (paragraph 0447), which Burchat et al. (2000) evidence are src kinase inhibitors (see Table 2). As such the pharmaceutical compositions of these specific compounds taught by Calderwood et al. and methods of treating edema using these specific compounds taught by Calderwood et al. anticipate the instant claims.

Claims 1, 2, 17, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Hirst et al. (US Patent Application 2002/0156081). The rejection is explained in the previous Office Action.

Applicants argue that Hirst et al does not provide an enabling disclosure of the presently claimed invention. Applicants argue that treatment of edema is discussed only generally in a laundry list of conditions in paragraph 315 of Hirst et al. and that the application states only that some of the compounds can be used to treat edema. Applicants argue that of the over 950 examples of compounds presented in Hirst et al. there is not a single data point of inhibition data. Only general allusions to unspecific activity against various diverse classes of tyrosine kinases is provided. This is not persuasive because despite the fact that treatment of edema is only one of several conditions to be treated Hirst et al. clearly teach the use of each of the 982 compounds of examples 1-982 for the treatment of edema and teach how to make each of these specific compounds. As such the use of each of these compounds is clearly enabled by Hirst et al. These examples include the specific compounds trans-Benzyl N-[4-[4-amino-1-[4-(4-

methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]carbamate (see paragraph 0686), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]benzamide (see paragraph 0697), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-2,2-dimethyl-3-phenylpropanamide (see paragraph 2549), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-3-methyl-3-phenylbutanamide (see paragraph 2562), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]benzo[b]furan-2-carboxamide, (see paragraph 2585), Trans-3-[4-(Benzylamino)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine, (see paragraph 0929) and trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-3-phenylpropanamide (see paragraph 1696) which Burchat et al. (2002) evidence are src kinase inhibitors (see Tables 3 and 4). As such the pharmaceutical compositions of these specific compounds taught by Hirst et al. and methods of treating edema using these specific compounds taught by Hirst et al. anticipate the instant claims.

Claims 3, 4, 19, 20, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calderwood et al (US Patent 6,001,839), Calderwood et al. (US Patent Application 2003/0187001) and Hirst et al. (US Patent Application 2002/0156081) in view of Hanke et al. The rejection is explained in the previous Office Action.

Applicants argue that the alleged structural similarity between the Calderwood compounds and PP1 and PP2 is superficial at best. The compounds of the Calderwood references are pyrrolopyrimidines, whereas PP1 and PP2 are pyrazolopyrimidines. The additional nitrogen in PP1 and PP2 relative to the Calderwood compounds could have a significant effect on activity and selectivity as inhibition of tyrosine kinases is highly unpredictable. In addition, the Calderwood compounds have a bulky phenoxy substituent on the phenyl ring, whereas PP1 and PP2 have relatively small methyl and chloro substituents on the phenyl ring. These differences could have significant effects on the selectivity as small changes in structure can lead to large changes in activity and selectivity. This is not persuasive as applicants arguments ignore the Hirst et al. reference entirely. The Hirst et al. reference teaches pyrazolopyrimidines and teaches the same utilities for these compounds as taught for the

pyrrolopyrimidine compounds of the Calderwood et al. references. The similarities in structure are clear and as all the compounds are disclosed for the same utilities the skilled artisan would believe other similar structures would have these same utilities. The similarity of the compounds PP1 and PP2 of Hanke et al., to the compounds of each of the three references, and in particular to the pyrazolopyrimidines of Hirst et al. is very clear. As such the skilled artisan would have a reasonable expectation that these compounds could be used in similar fashion. Applicants are reminded that obviousness does not require an absolute certainty of success but merely a reasonable expectation thereof. Furthermore, it should be noted that even if one were to conclude that there is not a reasonable expectation of treating edema with PP1 and PP2, the instant references would still make obvious claims 19, 20, and 32, as the combination clearly makes obvious a pharmaceutical composition of the Src kinase inhibitors of Hanke et al. for the treatment of cancer or osteoporosis as Hirst et al. clearly teach that Src kinase inhibitors are known to be useful for treatment of these conditions (see paragraph 0037). The intended use (as defined by the words on the label of Claims 19,

20, and 32) of a composition does not limit the composition itself. (see *In re Ngai*, 70 USPQ2d 1862).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652